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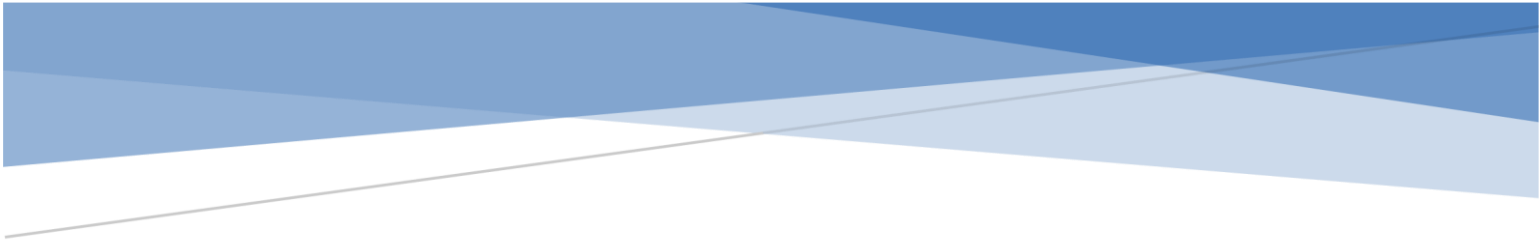
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CD4 + TH1 HELPER CELLS: THE UNIFYING LINK BETWEEN DIABETES AND PERIODONTITIS

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Topic: Molecular link between periodontitis and diabetes

Outline:

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Keywords

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Topic 1: Identify the cells present in the inflammation of patients with PD and T2D

Subtopic: The effects T2D has on the inflammation of Periodontal Diseases

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Abstract

Type II diabetes and Periodontitis are both chronic inflammatory diseases that affect people worldwide. Periodontitis is characterized by the obliteration of teeth. It affects 10-15% of adults and causes many problems on the quality of life (Preshaw et al., 2012). Diabetes is a disease that arises when your blood sugar is too high. Your blood glucose is the primary source of energy which is consumed by the food you eat. The hormone insulin is produced by the pancreas, which helps the glucose from allowing food to enter your cells. Many studies have shown that type 2 diabetes is a major risk factor for periodontitis and vice versa (Habib, 2018). In the presence of one disease increases the other and put them at risk for many other health related issues. Human research is very valuable regarding gaining more knowledge about these diseases, but the results have also been inconsistent (Okui, 2014).

As a result of the inconsistency researchers have identified the cells present in the inflammation of patients with Periodontitis and Type 2 diabetes, the effects Type 2 diabetes has on the inflammation in, and most importantly identifying the main cell produced in periodontitis that creates pro inflammatory cytokines. Knowing that CD4 T helper cells are the predominant cells found in gingival tissue from patients with type 2 diabetes. This is very helpful for future studies and researchers to better understand how the two diseases correlate with each other. This review will characterize the inflammation present in gingival tissue immune cells in people with Periodontitis and type 2 diabetes along with identifying the predominant cell type responsible to produce pro-inflammatory cytokines.

Keywords: Periodontitis, Diabetes, periodontal disease, CD4, TH1 cells, inflammatory cytokines,

Introduction

The link between diabetes and periodontitis has been studied immensely for more than 50 years (Mealey ,2006). “Periodontal disease is a chronic inflammatory disease that affects the tooth supporting periodontal bone and surrounding gingival tissue,” (Habib,2018). Most adults over the age of 30 are affected with this common disease. (Habib,2018). Periodontal disease can have a significant effect on the quality of life due to the destruction of alveolar bone (edentulism).

Type 2 diabetes (T2D) has a major affect for developing periodontal disease (Habib, 2018). According to the New CDC report “More than 100 million Americans have diabetes or prediabetes (New CDC, 2017). Patients with uncontrolled diabetes have been shown to have more gum disease than those without diabetes” (Gum Disease, 2013). Periodontal disease can worsen the severity of T2D by affecting glycemic control according to some reports (Habib, 2018). “The chronic inflammatory states of both conditions provide the connection for this two-way relationship between T2D and periodontal disease” (Grossi and Genco, 1998). Most studies have given evidence that one condition tends to increase the severity of the other or vice versa but many have failed to determine the molecular link between the two. As a result, the purpose of this review is to characterize inflammation present in gingival tissue immune cells in people

with and without T2D/PD and to determine the cell type responsible for the creation of pro-inflammatory cytokines.

Inflammation present in gingival tissue immune cells in subjects with PD

Bacterial elements produced in PD such as lipopolysaccharides, lipoteichoic acids, peptidoglycan, proteases and toxins initiate inflammatory responses in the in the periodontium (Habib,2018). The initial response of inflammation is initiated by TLR's (Toll- like receptors) on the outside of resident cells (Habib, 2018). TLR2 and TLR4 recognize these bacterial elements and their interactions with LPS initiate inflammation. If the response is unbalanced or excessive is may result in periodontal tissue destruction (Mesia, 2016). These TLR's recognize pathogens and activate the innate immunity due to invasion (Habib,2018). The pro-inflammatory cytokines produced are "IL-1, IL- 6, PGE2, and TNF- α ".

The effects T2D has on the inflammation of PD

Patients with diabetes have hyperinflammatory immune cells which can increase the production of pro-inflammatory cytokines (Mealey, 2006). The pro-inflammatory cytokines can cause insulin resistance and make it more difficult for the patient to control their diabetes. Salivary flow and burning mouth are characteristics in diabetes with poor glycemic control (Llambés, 2015). Delayed wound healing influences the inflammation present in PD which could then lead to sensory disorders, lesions and even tooth loss (Llambés, 2015). Diabetes slows down

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blood circulation which can make gums more prone to infection and reduces the body's ability to fight off the infection (Davenport, 2018). Patients with high glucose levels promote more growth of bacteria that causes periodontal diseases and lead to the pro-inflammatory cytokines. Advanced glycosylation end products (AGEs) in diabetes trigger an increase in inflammatory cells and studies show that AGEs bind to specific receptors on cells like fibroblast, and macrophages (Llambés, 2015). These macrophages transform into hyperactive cells that produce pro-inflammatory cytokines such as IL-6 and IL-1 β and TNF- α . AGEs also change the endothelial cells that will become hyperpermeable and hyper expressive. So the AGEs in diabetes produce chronic hyperglycemia which then produces hyper inflammatory responses, longer healing process, and higher exposure to infections. The activation of RAGE causes pathogenesis of PD in patients with T2D the activation of RAGE contributes to pathogenesis of periodontitis in diabetic patients (Llambés, 2015). AGEs reaction with RAGE lead to the production of pro-inflammatory cytokines.

Proinflammatory Cytokines within PD/T2D

The types of pro-inflammatory cytokines overlap in Type 2 diabetes and periodontitis. Type 2 diabetes is characterized by insulin resistance, glucose intolerance and low-grade chronic inflammation. Hyperglycemia is what drives Type 2 diabetes to inflammation which can also cause irreversible glycation of proteins leading to the formation of AGE's (advanced glycation end products). AGE's engage the receptor for advanced glycation end products (RAGEs) (Habib,2018). Engaging the RAGEs will activate inflammation and make people with T2D more susceptible to Periodontitis. An abnormal response known as hyper inflammatory trait happens within subject that have T2D and it can exaggerate the secretion of inflammatory mediators such

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as TNF- α and IL-6 (Hanes, 2010). Hyperglycemia in diabetic patients can lead to glycation of the structural proteins and lipids in the extracellular matrix, connective tissue and the vascular tissue. The changes in the vascular tissue leads to abnormal capillary function, damaged blood circulation, and the release in reactive oxygen species. This will result in a systematic inflammatory challenge which both periodontitis and diabetes have. Systematic inflammatory challenge is associated with chronic elevation of inflammatory mediators including IL-1, IL-6, TNF- α , fibrinogen, and C-reactive protein. The hyperinflammatory trait that is carried by diabetics results in more severe SIC (systemic inflammatory challenge). All the cytokines may be secreted by cells in response to stimulation by bacterial LPS's via TLR's. Infections such as periodontitis cause elevated levels of the cytokines which blocks lipoproteins lipase activity and make hyperlipemia. TNF α helps glycogenolysis and impairs glucose uptake, as well as targeting the hepatocytes to produce C-reactive proteins (Hanes,2010). These cytokines lead to both PD and T2D to be chronic and systematic inflammatory diseases.

Main Cells responsible for Cytokine production

Approximately 21 days after the initial innate host response the adaptive host response is mediated by T cells, B cells, and other antigen cell types (Habib,2018). B and T cells contribute to osteoclast activation which then leads to bone loss by the production of proinflammatory cytokines. T cells and B cells are specialized defender cells, they respond to different germs. When the body gets infected with a specific germ T and B cells will respond, quickly multiply and create an army of cells to fight against the infection. Some T and B cells will remember the

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invader that caused the infection and make the body immune to it the second time. Different types of T cells will have different jobs. Some send cytokines to the immune system and others kill the virus directly. Some also help B-cells make antibodies that circulate and bind to antigens. B cells make y shaped proteins called antibodies that stick to the antigens on the surface of germs stopping them from spreading and creating clumps that alert the body of invaders. This will then cause the body to make toxic substances to fight against them. The defender cells called phagocytes engulf and destroy the antibodies.

The role of B cells in PD/T2D

B cells play a huge role in both T2D and PD and could also be responsible for the unresolved inflammation within the two diseases. B cells act as antigen presenting cells (APC's) by internalizing antigens through surface immunoglobins (Habib,2018). The antigen degrades as a peptide and binds to class II molecules in the MHC (major histocompatibility complex) and then transported to the surface for CD4+ T helper cells. It was suggested that B cell antigen allows for activation and expansion of T cells (Habib,2018). B cells contribute to the severity of the PD and T2D. It is still unclear whether or not B cells are protective or pathogenic though, because they “facilitate bacterial clearance and contribute to halting disease progression” (Habib,2018),but most studies show that B cells “such as IL-10, IL-6, IL-8, IL-1 β , and TNF- α ” are one of the major sources of many anti-inflammatory cytokines in PD (Habib,2018). The amount of B cells in PD lesions shows that they hyper- produce cytokine activation and create the systematic inflammation in PD.B cells also produce RANKL which is a cytokine that promotes osteoclastogenesis (Habib,2018). Comparing both healthy and subjects with PD, B and T express

30-70% less RANKL in healthy gingiva than in PD Lesions (Habib,2018). B cells also contribute to osteoclastogenesis by regulating IL-6, which is the cytokine that promotes Th17. Th17 plays an important role in host defense against infection by recruiting macrophages and neutrophils to the tissues that are infected. The cytokines secreted by B cells in subjects with PD is very similar to the cytokines from B cells in subjects with T2D. High amounts of IL-8 were found in subjects with T2D while they were also unable to produce significant amounts of antiinflammatory IL-10. The subjects with PD were shown to have high concentrations of IL-8 and also high concentrations of IL-10. This data just shows that B cells are required for the expression of osteoclastogenic cytokines (Habib,2018).

The role of T cells in PD/T2D

T cells are required for alveolar bone destruction, deleting T cells from the body results in resistance to the disease (Habib, 2018). CD4⁺ T helper cells and CD8⁺ cytotoxic cells are the two subsets of T cells (Habib,2018). CD4⁺ T helper cells respond to antigen presentation by antigen peptide plus MHC class molecules that are expressed by APC's (Habib,2018). CD8⁺ cytotoxic T cells are vital for immune defense against intracellular pathogens, bacteria, and viruses. CD8⁺ T cells kill the infected cells through pro-inflammatory cytokines, but the role remains unknown (Habib,2018). Both CD4⁺ and CD8⁺ cells have been found in PD lesions but the main research has been on CD4⁺ T helper cells. CD4⁺ T helper cells function is to activate B cells to produce antigen specific antibodies. Lack of CD4⁺ T helper cells result in less bone resorption. Cytokine production by CD4⁺ regulates the inflammatory environment. Majority of the focus for this study although it presents CD8⁺ focuses on CD4⁺. CD4⁺ presented its function

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when the response of the mice to *P.Gingivals*. resulted in less bone resorption. The cytokines that CD4+ produce regulate the inflammation in Periodontitis (Habib, 2018). CD4+ T cells are vital for the effect of T-cells responding to pathogens (Graves, 2008). CD4+ T cells are classified into two subsets; Th1 and Th2 cell. The cytokines produced by the two subsets are referred to as Th1 cytokines, TNFa and IFN-g. These are critical for suppressing intracellular pathogens and are pro-resorptive through direct or indirect effects (Graves, 2008). The Th2 cells on the hand are not as pro-resorptive as the Th1 cells. In one of the methods the Th1 cells resulted in more intensive bone loss in mice that were stimulated with bacteria. The rats that were stimulated with the bacteria exhibited less bone loss because they received the adoptive transfer of Th2 cells (Graves, 2018). This data showed that the adaptive immune response depends on the T cells and the pro-inflammatory cytokines to help the effects of bone loss (Graves, 2018). Many studies researched the production of the Th1 and Th2 cytokines, but none studied the link it had with Periodontal bone loss until now. The impact of TNF-a was also examined where *P.gingivalis* was inoculated into the scalp of diabetic and normal mice (Graves, 2018). The impact of this bacteria caused bone resorption and bone formation which were both quantified. They tested the role of TNF-a with a specific inhibitor and the results of it after 2 days was new bone formation (Graves, 2018). They also showed that the mice treated with the TNF-a inhibitor compared to the one without. They also showed an increase in the duration of apoptosis of the bone lining cells. These studies allowed the researchers to identify where the inflammation is induced by bacteria. The increase in apoptosis of these cells could be linked to the immune response that is caused by the periodontal pathogens, which then causes impaired bone formation and leads to more bone loss (Graves, 2018). The evidence for altered T cell function in patients with Diabetes and Periodontitis is limited, but evidence does show a pattern in the cytokines in patients with PD

and T2D. This could possibly be related to the glycemic status and lead to more studies that focus on the Th1, Th2, TNF- α cytokines in T2D and PD.

Conclusion

Obesity and Type 2 diabetes affects people worldwide and increases chances of PD. As a result of the findings and data in this research it is very important that future researchers examine the immunopathogenesis of these diseases to develop better more effective methods of treatment, and prevention. Many of the studies done established that PD and T2D have a two-way relationship but didn't identify the molecular link between the two.

Some of the methods used in researches prior to this research were very limited and could only an estimation of what the cells function was. Using flow cytometry analysis allowed this research to quantify the number of cells from PD/T2D subjects that affect the inflammation in PD. The highest quantification of cells that was found in gingival tissue was CD4⁺ T helper cells that produced IL-2, IL-10, IFN- γ and TNF- α from subjects with T2D and PD (Habib, 2018). The cytokines produced suggest that pro- inflammatory Th1 cells are the predominant cell type in PD/T2D in gingival cells but not in gingival cells for the other two groups. This studied proved the thesis that type 2 diabetes does increase/effect the inflammation in Periodontitis. It is difficult to get quantified information for cytokine production, so this study exceeded and open the door for many more studies to be done. One limitation it had was not having gingival tissue samples from patients with just T2D. The data would've been more accurate and precise if samples from patients with just type 2 diabetes would've been included to have more to compare to. They could have also used more healthy subjects in ration to the patients with T2D and PD. Overall

this the study was well tested, and the data was clear and concise being that is was one of the first ones to test human subjects instead of animals. Hopefully more studies will continue and they have more subjects to compare the data to.

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